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EXAMINER	
LIU, SUE XU	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/963,698	BARANY ET AL.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *89-110,112 and 148-153* is/are pending in the application.

4a) Of the above claim(s) *98-108 and 110* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *89-97,109,112 and 149-153* is/are rejected.

7)☐ Claim(s) *89* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/08/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 1-88, 111 and 113-148 have been canceled.

Claims 89-110, 112 and 148-153 are currently pending

Claims 98-108 and 110 have been withdrawn;

Claims 89-97, 109, 112 and 149-153 are being examined in this application

Election/Restrictions

2. Claims 98-108, 110 are withdrawn from further consideration as acknowledged in the previous office actions.

Priority

3. This application is a divisional of application 08/794,851 (filed 2/04/1997; now US 6,852,487), which claims priority to US provisional application 60/011,359 (filed on 2/9/1996).

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-

filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No 60/011,359, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The instant claims have been amended to recite new features including "each have greater than sixteen nucleotides" and "capture oligonucleotide of the array differs in sequence from its adjacent… by at least 25% of the nucleotides", which do not appear to have support in the provisional application.

Thus, the instant claims 89-97, 109, 112 and 149-153 do not obtain the benefit of the early filing date of the provisional application.

Information Disclosure Statement

4. The information disclosure statement filed on 11/08/07 has been considered. See attached PTO 1449 form.

Claim Objection(s) / Rejection(s) Withdrawn

5. Upon further consideration, the following claim rejections as set forth in the previous office action are withdrawn:

A.) Claims 89-97, 109, 111, 112, 148-151 and 153 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claim Objection(s) / Rejection(s) Maintained

Claim Objections

6. Claim 89 is objected to because of the following informalities: The said claim 89 is missing a period "." at the end of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Second paragraph of 35 U.S.C. 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 89-97, 109, 111, 112 and 148-153 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below.

Claim 89 recites "selecting multimer nucleotides with nucleotide sequences differing from each other by at least 2 nucleotides, wherein no two dimers in a multimer are complementary to each other…" The instant claim 152 recites "the multimers" are "tetramers" as

set forth in "Table 1". However, at least some tetramers listed in Table 1 do not differ "by at least 2 nucleotide". For example, the listed number 1 and 2 tetramer in Table 1 has sequences, TGTC and TCTG respectively, which two sequences would not be considered to be differed by "at least 2 nucleotides" (the last two nucleotides of number 1 is the same as the first two nucleotides of number 2, and the first two nucleotides of number 1 is the same as the last two of number 2). In addition, all four nucleotides of number 1 is the same as the four nucleotides of number 2. Further, the last two nucleotides of number 16 (in Table 1) is "complementary to the first two nucleotides of number 8. As discussed above, recitation of the instant claim 89 seems to be in conflict with the recitation of claim 152. It is not clear what "multimer" and "dimer" are encompassed by the said claim limitation.

In addition, the term "a multimer" in line 11 of the instant claim 89 is unclear as to which entity the said term is referring. The instant claim 11 seems to use the term "multimer" or "multimer nucleotides" to refer to the building blocks that form the oligonucleotides on the solid support. However, the term "a multimer" in line 11 seems to refer to the oligonucleotides themselves because the claim language reciting "dimers in a multimer" (where the term "dimers" would refer to two multimer/multimer nucleotides building blocks that form the oligonucleotides on the array).

The instant claim 89 has been amended to recite "each have greater than sixteen nucleotides". It is not clear if the said phrase is referring to the "capture oligonucleotides" (i.e. each capture oligonucleotides have greater than sixteen nucleotides) or if the said phrase is referring to the "multimer nucleotides" (i.e. each multimer nucleotides have greater than sixteen nucleotides).

Discussion and Answer to Argument

10. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants assert the term "sequence" is defined and understood, and thus the instant claim 89 is not indefinite. (Reply, p.9).

Applicants are respectfully directed to the above modified rejection for discussion on how the said claim is indefinite. The instant claim 89 does not specifically define how the nucleotides sequences should be compared or alignment. Given the broad and reasonable interpretation of the instant claims, any alignment or comparison between two given multimers is appropriate. As discussed above, for example, the listed number 1 and 2 tetramer in Table 1 has sequences, TGTC and TCTG respectively, which two sequences would not be considered to be differed by "at least 2 nucleotides" (the last two nucleotides of number 1 is the same as the first two nucleotides of number 2, and the first two nucleotides of number 1 is the same as the last two of number 2). Contrary to applicant's assertion, the instant claim does not dictate that the comparison must be by aligning two multiple (from head to tail; or 5' end to 3').

Applicants are further respectively directed to the above rejection for discussion on additional issues due to claim amendments.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the e aminer presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Fodor and Others

13. Claims **89-97**, **109**, **112** and **149-153** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Fodor** et al (US Patent 5,510,270; 4/23/1996; earlier filing date 1992; cited previously), in view of **Brennan** et al (US 5,474,796; 12/12/1995) and **Froehler** et al (US 5,594,121; 1/14/1997; filing date 6/7/1995; cited in IDS). The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below.

The instant claims recite a method of forming arrays of oligonucleotides on a solid support comprising:

providing a solid support having an array of positions each suitable for attachment of an oligonucleotide;

attaching linkers to the solid support surface, wherein the linkers are suitable for coupling oligonucleotides to the solid support, at each of the array positions; and

forming an array of a plurality of capture oligonucleotides on the solid support by a series of cycles, each of the cycles comprising:

activating selected array positions for attachment of multimer nucleotides;

selecting multimer nucleotides with nucleotide sequences differing from each other by at least 2 nucleotides, wherein no two dimers in a multimer are complementary to each other and the multimers would not result in self-pairing or hairpin formulation; and

attaching the multimer nucleotides at the activated array positions, wherein the multimer nucleotides are selected so that the plurality of capture oligonucleotides formed by attachment of a plurality of the multimer nucleotides at each activated array position each have greater than sixteen nucleotides and have nucleotide sequences selected to hybridize with complementary oligonucleotide target sequences under uniform hybridization conditions across the array of oligonucleotides and so that each capture oligonucleotide of the array differs in sequence from its adjacent capture oligonucleotide, when aligned to each other by at least 25% of the nucleitdes, wherein the multimer is formed from multiple nucleotides linked together.

Fodor et al, throughout the patent, teach a method for synthesizing and screening oligonucleotides on a solid support (e.g. Abstract), which the solid support read the first step of **clm 89**. The method provides for the irradiation of a first predefined region of a substrate comprising immobilized nucleotides on its surface, without irradiation of a second predefined region of the substrate. The irradiation step removes a protecting group from the immobilized nucleotides. The substrate is contacted with a first nucleotide to couple the nucleotide to the immobilized nucleotides in the first predefined region without coupling in the second predefined region. At least a part of the first predefined region and at least a part of the second predefined region are subjected to further irradiation. The substrate is contacted with a second nucleotide, which couples to the immobilized nucleotides in at least part of the first and at least part of the second predefined regions. By repeating these steps, an array of diverse oligonucleotides is formed on the substrate (refers to the instant claimed method) (i.e., see abstract). The reference teachings read on the activating and attaching steps of **clm 89**. The reference also teaches using linker on the substrate for attaching nucleic acid probes onto the substrate (e.g. col.3, lines 1+), which read on the attaching linker step of **clm 89**.

Fodor et al use a mask to illuminate(or irradiate) selected regions of the substrate and uses photolithographic technique in synthesis of polymer arrays. Fodor et al teach that a square area is divided into square boxes, and the first reactions are carried out in the vertical columns and the process is repeated in the horizontal direction for the second unit of dimmer (i.e., see columns 18-19). Fodor et al teach that one mask can be used in al eight steps if it is suitably rotated and translated. For example, a mask with a single transparent region could be sequentially used to expose each of the vertical columns, translated 90^{0} and then sequentially used to allow exposure of the horizontal rows. Fodor et al teach that by controlling the locations of the substrate exposed to light and the reagents exposed to the substrate following exposure the locations of each sequence will be known (i.e., see column 9). The reference's teachings read on the method steps of **clm 90**.

Fodor et al teach that the substrate surface is composed of inorganicglass (i.e., see column 11), which reads on **clms 91-92**. Fodor et al teach that the substrate is conventional microscope slide or coverslip (i.e., see column 16) (refers to instant **clm 92**).

The reference also teaches the substrate having different positions and attached nucleic acid probes (e.g. Figure 10; cols.9+; col.15, lines 28+), which read on the different sequence on different positions of **clm 93**.

Fodor et al teach the solid support is substantially flat and may have wells, raised regions, etched trenches, or the like (i.e., see column 7, under substrate or in column 11), which reads on **clm 94**. The reference also teaches the substrate is a plate (e.g. col.11, lines 5+) and microtiter plate (e.g. col.2, lines 54+), which would render **clm 95** obvious because using microtiter plate as support for nucleic acid microarray is routine and known in the art as taught by Fodor et al.

The reference also teach functionalizing the substrate such as using silanized substrate (e.g. col.22, lines 54+), which reads on **clm 96**. Fodor et al teach that the surface of the substrate contains reactive groups which can be carboxyl, amino, hydroxyl (i.e., see column 11), which reads on **clm 97**.

Fodor et al teach that the any conceivable substrate may be employed in the invention. Fodor et al teach that the substrate is polymerized with gels or polymers such as (poly)tetrafluoroethylene, (poly)vinylidenedifluoride, polystyrene, polycarbonate (e.g. see column 11) as well as silanized substrate (e.g. col.22), which reads on **clm 109**.

The reference also teaches making polymers (including nucleotide probes) with different length such as greater than 16 nucleotides (e.g. cols.9-10, bridging), which reads on **clm 89**.

Fodor et al do not explicitly teach attaching "multimer nucleotides" to each activated position at each cycle of synthesis using "multimers" that are different "from each other by at least 2 nucleotides…" as recited in **clm 89**. The recitation "selecting multimer nucleotides with nucleotide sequences differing from each other by at least 2 nucleotides, wherein no two dimers in the multimers are complementary to each other…" is unclear and can be interpreted variously as discussed supra (see the Claim Rejection under 35 USC 112 2nd paragraph). The reference also does not explicitly teach a difference of "at least 25% of its nucleotides" and at least 6 nucleotides differences as recited in **clm 153**, barrier oligonucleotides recited in **clm 112**, using the various multimers as recited in **clms 149-152**.

However, Fodor et al, throughout the patent, teach the above discussed methods of making DNA microarray are applicable for making any DNA microarray with any nucleic acid sequence of desire or interest (e.g. col.10)

In addition, **Brennan** et al, throughout the patent, teach making and using various arrays (comprising various "sectors" (i.e. sub-arrays)) with various probes. The reference also teaches using arrays with 3-mers and 10-mers attached thereto such that the "total array presents every possible permutation of the 10-mer oligonucleotides" (col. 9, lines 48+). That is the taught array comprises all possible 3-mers or 10-mers that can be generated, and would provide probes that "differs from its adjacent capture oligonucleotides by at least 25%", because the all possible permutations of 10-mer oligonucleotides would encompass all different sequences. The all possible permutations would also encompass multimers different by at least 2 nucleotides.

Further, **Froehler** et al, throughout the patent, teach generating various nucleic acid probes by linking multimers together (e.g. col.6, lines 64+; col.10, lines 1+). The reference also teaches multimer with various lengths including "tetramer" (e.g. col.10, lines 1+). The reference also teaches making oligomers of greater than 40, 50 or 100 nucleomonomers (e.g. col.11, lines 45+). The reference also teaches various sequences can be generated for the oligomers. The reference also teaches the advantage of using "multimer" or oligomers to synthesize longer oligomers as the multimer intermediates offer valuable synthons for convenient synthesis of longer oligomers (e.g. col.10, lines 1+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to link "multimers" (or oligomers) with various lengths

(including "tetramers") and desired sequences together to form longer oligomers as nucleic acid probes on nucleic acid arrays.

A person of ordinary skill in the art would have been motivated at the time of the invention to using oligomers with at least 2 nucleotides difference as building blocks for generating longer oligomers on an array, because Brennan et al teach making probes with different sequences (or all possible permutations) are routine and known in the art, Fodor also teaches making array with desired sequences are routine and known in the art, Froehler teaches linking various oligomers (with various lengths such as greater than 40 nucleotides and sequences) together to form longer oligomers are routine and known in the art. Because all of the cited references teach methods making DNA microarray (including making probes) or making various DNA probes with various desired sequences, it would have been obvious to one skilled in the art to substitute one type of probes (with one type of sequences) for the other (with sequences differ by at least 2 nucleotides) to achieve the predictable result of making nucleic acid arrays with the desired nucleic acid sequences for various experimental purposes such as to reduce cross-reactivity among the attached probes (and therefore improve accuracy of the detections). It would have been obvious to one skilled in the art to substitute one type of probes (with one type of sequences) for the other (with sequences differ by at least 25% of its nucleotides or at least 6 nucleotides) to achieve the predictable result of making nucleic acid arrays with the desired nucleic acid sequences for various experimental purposes such as to reduce the formation of hairpins in the probes themselves.

A person of ordinary skill in the art would have been motivated at the time of the invention to generate "barrier oligonucleotides" adjacent to the "capture oligonucleotides",

because all of the cited references teach oligonucleotides with various lengths and sequences can be generated using known and routine methods. In addition, Fodor also teaches attaching specific oligonucleotides at specific position on an array is also routine and known in the art. Thus, It would have been obvious to one skilled in the art to substitute one type of probes (with one type of sequences) for the other (with shorter nucleotide lengths) to achieve the predictable result of making nucleic acid arrays with the desired nucleic acid sequences for various experimental purposes such as to improve the cross-reactivity of the attached probes.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of making nucleic acid arrays and generate nucleic acid probes using various building blocks such as mulitmers/oligomers with different sequences.

Discussion and Answer to Argument

14. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants traversed the above rejection by mainly arguing each reference alone does not teach all elements of the instant claimed invention. (Reply, pp. 9+).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue the Brennan reference "fails to exclude the use of timers or 10-mers which contain complementary dimers..." and "differs...by at least 25%". Applicants also provided alignments of sequences from Brennan. (Reply, p.10).

First, the above rejection is over the combination of the cited references, and not just over the Brennan reference alone. As discussed supra, the cited combination of references renders the instant claimed invention obvious.

It is also not clear which sequences from the Brennan reference were used for the alignment comparison by applicants. It appears applicants the first sequence in applicant's alignment is the "DNA Fragment" in Figure 1C of the Brennan reference. It is not clear where the second sequence (allegedly a probe on the array) is from. Contrary to applicant's assertion, the sequence indicated as "DNA Fragment" in Brennan is a "target nucleic acid sequence", but not a sequence that was placed on the DNA array. The said Figure 1C illustrates how a sequence of the target nucleic acid can be deciphered from trimer hybridization (see col.10), and it does not provide information on the DNA probes that are attached to the DNA array.

Similarly, applicants also argue the Froehler reference also does not teach the all elements of the instant claim. Applicants especially argue the Froehler reference does not teach "the synthons must not contain complementary dimers and must not undergo self pairing…" As discussed above, the cited references (including Froehler, Brennan and Fodor) teach it is routine, known, and predictable in the art, to make probes with different sequences (such as all possible permutations), to make array with any desired sequences, and to link various oligomers (with various lengths such as greater than 40 nucleotides and sequences) together to form longer oligomers. It would have been obvious to one skilled in the art to substitute one type of probes

(with one type of sequences) for the other (with sequences differ by at least 25% of its nucleotides or at least 6 nucleotides, or probes that would not be self complementary and/or self pairing, etc.) to achieve the predictable result of making nucleic acid arrays with the desired nucleic acid sequences for various experimental purposes such as to reduce the formation of hairpins in the probes themselves. It is within purview of one of ordinary skill in the art, to try various combinations of nucleic acid sequences., in an attempt to optimize nucleic acid probes, depending on the needs of various routine experimental designs, as a person with ordinary skill has good reason to pursue the known options within his or her technical grasp.

Holmes and Others

15. Claims **89-94**, **96-97**, **109**, **112** and **149-153** are rejected under 35 U.S.C. 103(a) as being unpatentable over **HOLMES** et al (US Patent 5,527,681; 6/18/1996; filed 11/5/1992; cited previously), in view of **Brennan** et al (US 5,474,796; 12/12/1995) and **Froehler** et al (US 5,594,121; 1/14/1997; filing date 6/7/1995; cited in IDS). The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below.

Holmes et al teach a synthetic strategy for the creation of large scale chemical diversity using solid phase chemistry, photo labile protecting groups and photolithography achieve light directed spatially addressable parallel chemical synthesis of an array of polymers (i.e., see abstract). Holmes teaches that the preferred embodiment provides for the synthesis of an array of polymers in which individual monomers in a lead polymer are systematically substituted with monomers from one or more basis sets of monomers. The reference teaches that the substrate is

flat and it may have synthesis regions separated by structures, and the surface may have wells, raised regions, or etched trenches (i.e., see column 5). The reference teaches that the substrate has linker molecules, which are optionally protected with photo removable protecting groups. The reference teaches that the mask is used and rotated for the following coupling steps. The reference claims and specification disclosure are drawn to a method of synthesizing an array of oligonucleotides on a surface of a substrate clearly anticipates the claimed invention.

Holmes et al teach the substrate with surface, and optional Linker molecules are provided on the surface (i.e., see column 7).

The reference teaches thus formed oligonucleotide array will have variety of uses including, screening large number of polymers for biological activity by exposing the array to receptors. The receptor chosen can be a nucleic acid sequence (i.e., see column 4, definition of receptor). And the reference claim recites that the oligonucleotide array is contacted with a receptor (nucleic acid) to identify an oligonucleotide complementary to said receptor (refers to the oligonucleotide target sequence). NOTE In the claimed method of forming array of oligonucleotides, the limitation 'the capture oligonucleotides on the array hybridize with complementary oligonucleotide target sequences under uniform conditions' is considered as the intended use of thus formed array, not the method step. Thus the reference clearly anticipates the claimed invention.

The reference teaches generating probes with various lengths, for examples, between 2-20 nucleotides (cols. 9. lines 20+), which reads on the length as recited in the instant claim 148.

Holmes et al do not explicitly teach attaching "multimer nucleotides" to each activated position at each cycle of synthesis using "multimers" that are different "from each other by at

least 2 nucleotides…" as recited in **clm 89**. The recitation "selecting multimer nucleotides with nucleotide sequences differing from each other by at least 2 nucleotides, wherein no two dimers in the multimers are complementary to each other…" is unclear and can be interpreted variously as discussed supra (see the Claim Rejection under 35 USC 112 2nd paragraph). The reference also does not explicitly teach a difference of "at least 25% of its nucleotides" and at least 6 nucleotides as recited in **clms 89** and **153**, barrier oligonucleotides recited in **clm 112**, using the various multimers as recited in **clms 149-152**.

However, Holmers et al, throughout the patent, teach the above discussed methods of making DNA microarray are applicable for making any DNA microarray with any nucleic acid sequence of desire or interest (e.g. Figures 1-2) .

In addition, **Brennan** et al, throughout the patent, teach making and using various arrays (comprising various "sectors" (i.e. sub-arrays)) with various probes. The reference also teaches using arrays with 3-mers and 10-mers attached thereto such that the "total array presents every possible permutation of the 10-mer oligonucleotides" (col. 9, lines 48+). That is the taught array comprises all possible 3-mers or 10-mers that can be generated, and would provide probes that "differs from its adjacent capture oligonucleotides by at least 25%", or by at least 6 nucleotides because the all possible permutations of 10-mer oligonucleotides would encompass all different sequences. The all possible permutations would also encompass multimers different by at least 2 nucleotides.

Further, **Froehler** et al, throughout the patent, teach generating various nucleic acid probes by linking multimers together (e.g. col.6, lines 64+; col.10, lines 1+). The reference also teaches multimer with various lengths including "tetramer" (e.g. col.10, lines 1+). The reference

also teaches making oligomers of greater than 40, 50 or 100 nucleomonomers (e.g. col.11, lines 45+), which reads on the greater than 16 nucleotides in length. The reference also teaches various sequences can be generated for the oligomers. The reference also teaches the advantage of using "multimer" or oligomers to synthesize longer oligomers as the multimer intermediates offer valuable synthons for convenient synthesis of longer oligomers (e.g. col.10, lines 1+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to link "multimers" (or oligomers) with various lengths (including "tetramers") and desired sequences together to form longer oligomers as nucleic acid probes on nucleic acid arrays.

A person of ordinary skill in the art would have been motivated at the time of the invention to using oligomers with at least 2 nucleotides difference as building blocks for generating longer oligomers on an array, because Brennan et al teach making probes with different sequences (or all possible permutations) are routine and known in the art, Holmes also teaches making array with desired sequences are routine and known in the art, Froehler teaches linking various oligomers together to form longer oligomers are routine and known in the art. Because all of the cited references teach methods making DNA microarray (including making probes) or making various DNA probes with various desired sequences, it would have been obvious to one skilled in the art to substitute one type of probes (with one type of sequences) for the other (with sequences differ by at least 2 nucleotides as well as with greater than 16 nucleotides) to achieve the predictable result of making nucleic acid arrays with the desired nucleic acid sequences/length for various experimental purposes such as to reduce cross-reactivity among the attached probes (and therefore improve accuracy of the detections). It

would have been obvious to one skilled in the art to substitute one type of probes (with one type of sequences) for the other (with sequences differ by at least 25% of its nucleotides or at least 6 nucleotides as well as with >16 nucleotides long) to achieve the predictable result of making nucleic acid arrays with the desired nucleic acid sequences for various experimental purposes such as to reduce the formation of hairpins in the probes themselves.

A person of ordinary skill in the art would have been motivated at the time of the invention to generate "barrier oligonucleotides" adjacent to the "capture oligonucleotides", because all of the cited references teach oligonucleotides with various lengths and sequences can be generated using known and routine methods. In addition, Holmes also teaches attaching specific oligonucleotides at specific position on an array is also routine and known in the art. Thus, It would have been obvious to one skilled in the art to substitute one type of probes (with one type of sequences) for the other (with shorter nucleotide lengths) to achieve the predictable result of making nucleic acid arrays with the desired nucleic acid sequences for various experimental purposes such as to improve the cross-reactivity of the attached probes.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of making nucleic acid arrays and generate nucleic acid probes using various building blocks such as mulitmers/oligomers with different sequences.

Discussion and Answer to Argument

16. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants traversed the above rejection with the same argument as the traversal over Fodor and others. Thus, applicants are respectfully directed to the discussion under the Fodor and others for answer to arguments.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 89 and 149-151 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 7,455,965.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed invention of the '965 patent reads on the instant claimed invention.

The '158 application claims a method of making a substrate by attaching various nucleic acid probes through linking "multimers" together on the substrate (claim 1), which the substrate read on an array, and the capture probes read on the capture probes of the instant claim 89.

The '158 application also teaches linking the tetramers together on various positions on the solid support (see claims 1 and 2), which read on the cycles of attaching multimers to the solid support of the instant claim 89.

The '158 application also claims using linkers and the multimers are "tetramers" (claim 1), which read on the tetramer of the instant claims 149-151.

Thus, the claimed invention of the '158 application reads on or is obvious over the instant claimed invention.

Discussion and Answer to Argument

19. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants assert the inventions claimed in the '965 patent is different from the instant claimed invention. (Reply, p.12).

Applicants seem to argue because the '965 patent recites additional steps such as "randomized, divided into first and second…", the '965 patent does not read on the instant claimed invention. However, the instant claims are broad and encompassing various method

steps and reagents. The instant claim 89 recites the transition phrase "comprising" which is open-ended and do not exclude additional steps. As discussed supra, the '965 patent teaches methods of making a DNA array having various probes with desired sequences. Thus, the above rejection is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/
Primary Examiner, Art Unit 1639
4/23/09